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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,369	12/26/2006	Philippe Dupraz	ARS.126	2134

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EXAMINER	
MARVICH, MARIA	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
09/13/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/573,369	**Applicant(s)** DUPRAZ ET AL.	
	Examiner MARIA B. MARVICH	**Art Unit** 1633	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 30 August 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *50 and 52*.
   Claim(s) objected to: _____.
   Claim(s) rejected: *45-49,51 and 53-56*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Maria B Marvich/
Primary Examiner, Art Unit 1633

Continuation of 11. does NOT place the application in condition for allowance because: applicants' arguments are not persuasive for the following reasons. First, applicants argue that there would be no motivation to combine Ashkenazi et al and Patel et al to arrive at the instantly constructed IgSP-tPA (tPA-pre-propeptide). Rather, following the teachings of Ashkenazi et al and Patel et al, the combination would have resulted in replacement of the tPA-pre-propeptide with the IgSP sequence.

To the contrary, the teachings of Ashkenazi et al are direct a person of skill when designing constructs to improve protein yield to use of a combination "signal pro-sequence". Ashkenazi teaches that tPA provides both signal and pro functions wherein these functions are to bind to the signal recognition particle and direct the protein to the lumen of the ER. pTA mediates this function by the signal sequence and pro-sequence of tPA wherein these seqeunces mediate export and secretion (see abstract and page 2, line 14). Furthering this idea, Ashkenazi states on page 2, line 33, that a DNA segment is coupled to a heterologous sequence wherein the DNA segment comprises a mammalian signal and or pro-peptide. To this end, tPA can mediate both functions or one may use "alternativley a heterologous signal and or pro-sequence". This establishes that Ashkenazi recognizes that these functions are separable. . Applicants further this concept by developing a tPA-pre-propeptide wherein the tPA pro-sequence is linked to a signal sequence from TNFR. Regarding the scope of signal sequences, Ashkenazi does not limit use ot TNFR signal sequence and allows that any signal sequence can be used. "According to this aspect of the invention, the mammalian t-PA signal sequence or other hetrologous signal signal and or pro-sequence and the pro-peptide amino acid seqeunce comprise the precursor peptide of the invention (page 2-3, bridging sentence)." Ashkenazi clearly establishes that a first DNA segment that is a precursor peptide comprises seperable elements that mediate export (signal seqeunce) and secretion (pro-sequence). "A "precursor peptide" as used in the context of the present invention and as more fully described below, is used to refer to a polypetpide have an amino acid seqeunce corresponding to all or a portion of a naturally occurring mammalian t-PA signal and/or pro-peptide which participates in the secretion of t-PA under native conditions (page 6)."A signal-pro sequence is defined as one comprising the signal sequence and the pro-peptide" and and while the heterologous signal sequence embodied in Ashkenazi et al is TNFR, the option is open to use of any other signal sequence (see e.g. page 12, line 25-28).

This advances the art of Patel et al which teaches only linkage of signal sequences such as that from IgSP to heterologous sequences for secretion (see e.g. page 14, line 22 and figure 15A). One would have been motivated to combine the two given that the combination improves secretion and export of heterologous sequences over use of just the signal peptide. To do so overcomes intracellular retention of proteins and facilitates extracellular recovery of the produced protein (see AShkenazi et al, page 2, line 8-10).

Secondly, applicants argue that the specification teaches that the property of the instant pre-proseqeunce is unexpected and for evidence point to figure 4 which is described in example 1.2. Figure 4 demonstrates that use of tPA pro seqeunce in combination with IgSP increases levels of TBP (heterologous protein) in the lysate of cells by 1 fold over use of just IgSP. However, the results of IgSP-tPA versus IgSP does not take into consideration the effect of tPA. “In this case, greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue.” In re Corkill, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). In Corkhill, the claimed combination showed an additive result when a diminished result would have been expected. This result was persuasive of nonobviousness even though the result was equal to that of one component alone. Evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating “synergism”). Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). However, a greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage.” In this case, it is not clear that the the effects of tPA pro-sequence with IgSP would not have been expected given that Ashkenazi recognizes that a signal sequence and tPA pro-sequence are desired to lead to increased elves of secreted protein. In other words, the comparison should be IgSP-tPA versus TNFR-tPA with an indication that an increase over these levels by IgSP would nto have been expected.